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ANION SECRETION BY THE ISOLATED RABBIT PANCREAS

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The isolated rabbit pancreas secretes a fluid containing chloride and bicarbonate in about equal concentrations. Replacement of bicarbonate by acetate, phosphate or isethionate, replacement of Na^+ by Li^+ and addition of ouabain to the bathing medium of the pancreas inhibit the secretion of fluid, chloride and bicarbonate in a similar fashion and by maximally 100%. Replacement of chloride by isethionate inhibits fluid secretion by maximally 50%, chloride secretion by 90% and bicarbonate secretion by 20%. It is concluded that fluid secretion is based on a Na^+-gradient-dependent bicarbonate influx or proton efflux in the ductular cell, and that the secretion of chloride is secondary to that of bicarbonate.

Introduction

The pancreas secretes an isotonic fluid containing water, electrolytes and enzymes. The origin of water and electrolytes seems to differ between species. In all species the ductular cells secrete a bicarbonate-rich secretory fluid, which process is stimulated by the polypeptide hormone secretin. In some species, e.g. the rat, there is an additional secretion of a chloride-rich secretory fluid by the acinar cells, which process is stimulated by cholecystokinin-pancreozymin and acetylcholine [1,2]. In other species, like cat and dog, the acinar cells apparently do not contribute to the fluid secretion process [3]. In addition, in the main pancreatic duct a chloride-bicarbonate exchange mechanism is present, which leads to a decrease of the bicarbonate concentration and to an increase of the chloride concentration at decreasing secretory rate [4,5]. The composition of the secretory fluid at high secretory rates seems to reflect the contribution of both cell types to the secretion process. In the cat the bicarbonate concentration may go up to 140 mM [6], in the rat only to 80 mM [1].

The isolated rabbit pancreas spontaneously secretes a fluid with a bicarbonate concentration of 70–90 mM. The rate of fluid secretion is not stimulated by cholecystokinin-pancreozymin and acetylcholine and is only slightly stimulated by secretin [7]. Previous studies in this laboratory have investigated the role of sodium in this process by application of ouabain [7], replacement of sodium [8] and hyperosmotic addition of sodium chloride [9]. From the findings reported in these papers and the fact that the $(Na^+ + K^+)$-ATPase is localized in the basolateral plasma membrane of both cell types [10], we conclude that fluid and electrolyte secretion is driven in rate-limiting fashion by the $(Na^+ + K^+)$-ATPase system, via the establishment of a Na^+ gradient. This gradient would lead by means of a sodium anion co-transport or counter-transport mechanism to the accumulation of anions in both cell types. The anions, bicarbonate in the ductular cell and chloride in the acinar cell, would than passively leave the cells through the apical plasma membrane with the parallel movement of Na^+ and K^+ through a paracellular route. The low maximal bicarbonate concentration in the secretory fluid of the rabbit pancreas led us to suggest that both ductular and

acinar cells would contribute to the secretory process.

In order to test this model we have studied the effects of anion replacements on the rate of fluid secretion and the anion composition of the secretory fluid. Our findings suggest that despite the low maximal bicarbonate concentration in the rabbit pancreas the entire fluid secretion appears to originate from one cell type, presumably the ductular cell.

Methods

Male and female New Zealand white rabbits of 3–4 kg are used. The animals are killed by a blow on the neck, immediately followed by exsanguination. The pancreas is prepared essentially as described by Rothman [11] and modified by us [12,13]. The isolated pancreas is mounted on a frame and incubated in a bath containing 350 ml of bathing medium. The main pancreatic duct is cannulated close to its junction with the duodenum, and the secreted fluid is collected. The isolated pancreas is preincubated for 1 h after mounting in a balanced Krebs-Ringer bicarbonate medium in order to reach a steady-state condition. The composition of the normal Krebs-Ringer bicarbonate (KRB) medium is (in mmol/l): NaCl 118.5, KCl 3.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 5.5 (pH 7.4). The medium is continuously gassed with carbogene (95% O_2, 5% CO_2). After the preincubation the medium is replaced by fresh Krebs-Ringer bicarbonate medium and the experiment is started. The secreted fluid is collected in 10-min fractions in preweighed plastic tubes. The fractions, in which the bicarbonate concentration is to be measured, are collected under paraffin oil. From each fraction aliquots are taken for the appropriate assays.

The bicarbonate and chloride replacement studies are carried out as follows: After 1 h of incubation in the normal medium (control period), the medium is replaced by a low bicarbonate medium in which $NaHCO_3$ is partly or wholly replaced by equimolar concentrations of sodium acetate, phosphate or isethionate, or by a low chloride medium in which NaCl is replaced partly or wholly by sodium isethionate and KCl, $MgCl_2$ and $CaCl_2$ by their sulphates. The low bicarbonate media are brought to pH 7.4 by gassing with an appropriate mixture of carbogene and O_2, the mixture ratio being determined empirically. The media without bicarbonate are gassed with 100% O_2. The pH of the medium is continuously recorded and, when necessary, adjusted to pH 7.4 by titration with NaOH or HCl. The amounts of sodium and chloride thus added are too small to cause a measurable change in the sodium or chloride concentration.

In the Na^+ replacement studies, the normal medium is replaced by a low Na^+-KRB medium with NaCl partly replaced by equimolar concentrations of LiCl.

The experiments generally comprise a control period of 60 min followed by two experimental periods of 60–90 min, and sometimes an additional 60-min control period. In the experimental period a replacement anion or inhibitor is added in increasing concentration. The secretory rate and the composition of the secreted fluid reach a steady level within 30–60 min. In the control period the medium consists of a normal Krebs-Ringer bicarbonate medium. A sample of the bathing medium is taken every 30 min for determination of the ion concentrations. For calculations the mean values are taken of the final 30 min of the control period and of each experimental period.

Assay methods

The volume of the secreted fluid fractions is determined by weighing on a fully automatic Mettler electronic balance, assuming the density of the fluid to be 1.0.

Na^+ and K^+ concentrations are measured by flame photometry in an Eppendorf flame photometer. Samples of 10 or 15 μl bathing medium or pancreatic fluid are diluted with distilled water to 3 ml. Standard solutions containing NaCl and KCl in the same concentration range are used for calibration curves, which are virtually linear.

Chloride is determined coulometrically. A 5- or 7.5-μl sample of bathing medium or secreted fluid is diluted with 3.5 ml dilution medium containing 10% acetic acid and 0.1 M nitric acid. Three drops of a gelatin indicator solution are added and the chloride content of the sample is measured by titration in an Aminco-Cotlove chloride titrator. Standards and blanks are titrated prior to the

samples. The Cl^- concentration of the samples is calculated from the titration time after correction for the blank.

The bicarbonate concentration of the fluid fractions collected under oil is determined by measuring the total CO_2 content in a Natelson microgasometer. A 10- or 20-µl sample is mixed with an equal volume of lactic acid to liberate all CO_2 from the sample. The CO_2 is then absorbed by NaOH and the CO_2 content of the sample is calculated from the difference in pressure before and after CO_2-absorption. In the experiments with ouabain and in the Na^+-replacement experiments, the bicarbonate concentration in the secreted fluid is calculated as the difference between the ($Na^+ + K^+$) concentration and the chloride concentration.

The acetate or isethionate concentrations of the secreted fluid fractions from the experiments, where bicarbonate is replaced by these anions, are estimated as the difference between the ($Na^+ + K^+$) concentration and the ($Cl^- + HCO_3^-$) concentration of the fractions.

The phosphate concentration in the secreted fluid, where bicarbonate in the medium has been replaced by phosphate, is measured by the method of Fiske-SubbaRow [14].

Results

In normal Krebs-Ringer bicarbonate medium, the secretory rate of the isolated rabbit pancreas remains constant for about 6 h after isolation. The Cl^- concentration in the secreted fluid is 72 mM (S.E. 1.3, $n = 66$) and the HCO_3^- concentration is 82 mM (S.E. 1.9, $n = 19$). The Na^+ and K^+ concentrations are about equal to those in the bathing medium and their sum is not significantly different from the sum of Cl^- and HCO_3^-.

When HCO_3^- in the bathing medium is completely replaced by acetate, phosphate or isethionate, the fluid secretion rate is reduced by 43, 69 or 85%, respectively (Table I), while the HCO_3^- concentration in the secreted fluid decreases and the Cl^- concentration increases (Fig. 1). Acetate, estimated as the difference between the sum of the cation concentrations ($Na^+ + K^+$) and the anion concentrations ($Cl^- + HCO_3^-$) appears in the secreted fluid in a lower concentration (33 mM) than HCO_3^- in the control period (82 mM). Isethionate hardly appears in the secreted fluid (calculated value: 2.9 mM, S.E. 2.8, $n = 6$). The measured phosphate concentration in the secreted fluid in the phosphate replacement ex-

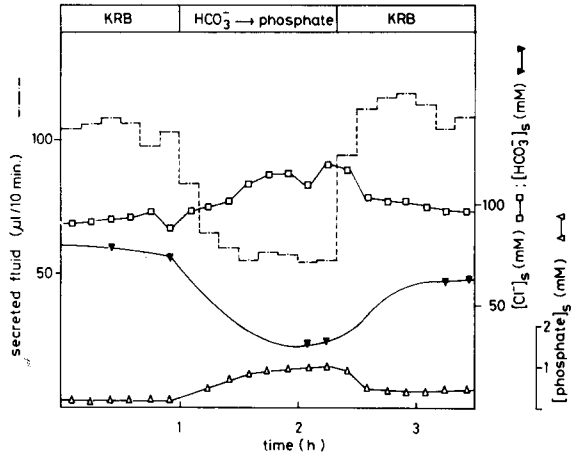

Fig. 1. Effect of replacement of bicarbonate by phosphate on the rate of fluid secretion (·–·–·) and on the concentrations of HCO_3^- (▼——▼), Cl^- (□——□) and phosphate (△——△) in the secreted fluid of the isolated rabbit pancreas.

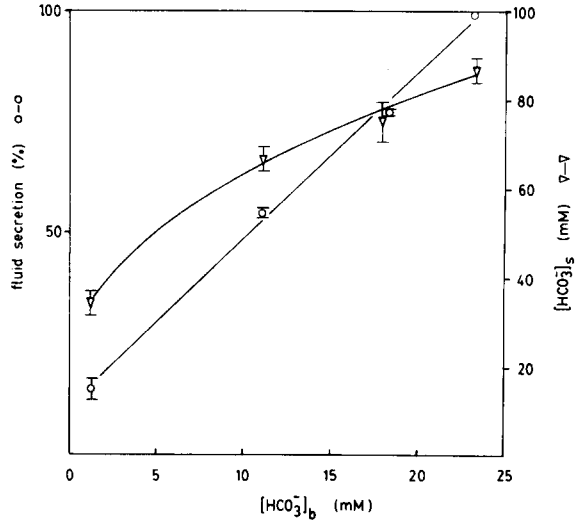

Fig. 2. Effect of bicarbonate concentration in the bathing medium on the rate of fluid secretion (○——○) and the HCO_3^- concentration in the secreted fluid (▽——▽). HCO_3^- is replaced by equimolar concentrations of isethionate. The results on fluid secretion are expressed as percentage of the fluid secretion rate in the presence of HCO_3^- and represent mean values ± S.E. For the number of experiments see Tables I and II.

TABLE I

EFFECTS OF HCO_3^--, Cl^--, Na^+-REPLACEMENT AND OF OUABAIN ON THE RATE OF FLUID SECRETION AND THE ANION CONCENTRATIONS IN THE SECRETED FLUID

Mean values ± S.E. are given, *N*, number of experiments.

	N	Residual fluid secretion rate (% of control)	Cl^- (mM)	HCO_3^- (mM)	Acetate (mM)	Phosphate (mM)	Isethionate (mM)
No replacement		100	72	82	–	–	–
Complete replacement of HCO_3^- by:							
Acetate	9	57 ± 4	92 ± 3	27 ± 1	33 ± 4 [a]	–	–
Phosphate	5	31 ± 6	111 ± 4	31 ± 1	–	2.9 ± 1.0	–
Isethionate	6	15 ± 2	127 ± 5	34 ± 4	–	–	2.9 ± 2.8 [a]
Complete replacement of Cl^- by:							
Isethionate	8	50 ± 3	15 ± 2	130 ± 7	–	–	15 ± 6 [a]
Partial replacement of Na^+ by Li^+:							
Na^+ (mM) / Li^+ (mM)							
112 / 38	4	69 ± 3	69 ± 5	83 ± 5 [a]	–	–	–
93 / 60	4	62 ± 5	80 ± 2	72 ± 3 [a]	–	–	–
68 / 76	5	55 ± 2	78 ± 4	69 ± 6 [a]	–	–	–
36 / 105	14	31 ± 3	95 ± 2	52 ± 3 [a]	–	–	–
Addition of:							
Ouabain (10^{-6} M)	6	70 ± 2	98 ± 5	67 ± 4 [a]	–	–	–
Ouabain (10^{-5} M)	7	20 ± 2	132 ± 3	29 ± 3 [a]	–	–	–

[a] Calculated value assuming $Na^+ + K^+ = Cl^- + HCO_3^-$ + replacing anion.

periments is also very low (2.9 mM, S.E. 1.0, $n = 5$; Table I). The Na^+ and K^+ concentrations in the secreted fluid do not change significantly in the course of the HCO_3^--replacement experiments.

HCO_3^- is never completely absent from the secreted fluid. When HCO_3^- is completely replaced by acetate, phosphate or isethionate, its concentration in the bathing medium during incubation still reaches up to 3 mM, presumably due to incomplete washing out of the tissue. The HCO_3^- concentration in the secreted fluid then reaches up to about 30 mM, probably due to the residual HCO_3^- in the bathing medium, or to HCO_3^- derived from metabolically produced CO_2 in the pancreas preparation. The relation between the HCO_3^- concentrations in the bathing medium and in the secreted fluid and the secretory flow rate is shown in Fig. 2. The data are taken from the experiments in which HCO_3^- is partially or fully replaced by isethionate, since this anion is least effective in replacing HCO_3^- and is virtually not secreted.

Complete replacement of Cl^- by isethionate causes 50% reduction in the fluid secretory rate, a decrease of the Cl^- concentration of the secreted fluid to 15 mM and an increase of the HCO_3^- concentration to 130 mM (Table I). The increase of the HCO_3^- concentration does not entirely compensate for the reduction of the Cl^- concentration, the anion deficit presumably being balanced by isethionate. At full Cl^- replacement 15 mM isethionate is calculated to appear in the secreted fluid (Table I). Fig. 3 shows the effects of decreasing the Cl^- concentration of the bathing medium on the Cl^- concentration of the secreted fluid and on the flow rate. The data are from experiments with partial or full replacement of Cl^- by isethionate.

Upon partial replacement of Na^+ by Li^+, the secretory flow rate decreases, the Cl^- concentration of the secreted fluid increases and the HCO_3^- concentration decreases (Table I). These effects increase with increasing replacement of Na^+. In the low-Na^+ media, the Na^+ and Li^+ concentra-

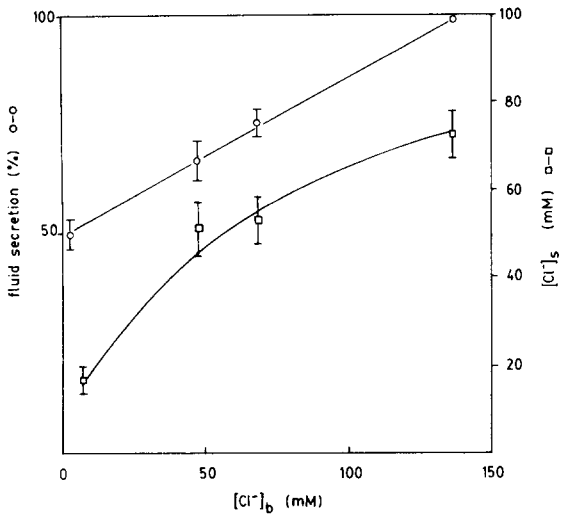

Fig. 3. Effect of chloride concentration in the bathing medium on the rate of fluid secretion (○———○) and the Cl^- concentration in the secreted fluid (□———□). Cl^- is replaced by equimolar concentrations of isethionate. The results shown represent mean values ± S.E. For the number of experiments see Tables I and II.

tions of the secreted fluid are virtually equal to those in the bathing medium, but the K^+ concentration tends to rise slightly. Upon the addition of ouabain to the bathing medium, the secretory flow rate decreases, the Cl^- concentration of the secreted fluid increases and the HCO_3^- concentration decreases (Table I). The effect of ouabain is also concentration-dependent. In the presence of ouabain, the Na^+ concentration of the secreted

TABLE II

EFFECTS OF REPLACEMENT OF HCO_3^-, Cl^- OR Na^+ AND ADDITION OF OUABAIN ON THE INHIBITION OF FLUID, Cl^-, AND HCO_3^- SECRETION

For the replacement experiments, the measured values for the HCO_3^-, Cl^-, phosphate, Na^+ and Li^+ concentrations in the bathing medium are shown. Mean values ± S.E. are given. *N*, number of experiments.

Experiment	Medium concentration			*N*	% Inhibition of		
	HCO_3^-	Cl^-	Replacing anion [a]		Fluid secretion	Cl^- secretion	HCO_3^- secretion
Normal Krebs-Ringer bicarbonate medium	24	134	0	19	0	0	0
HCO_3^- replacement							
by isethionate	17.9	134	6.1	2	27 ± 1	13 ± 1	33 ± 1
by isethionate	11.1	134	12.9	2	47 ± 2	29 ± 5	59 ± 1
by isethionate	1.1	134	22.9	6	85 ± 2	71 ± 1	94 ± 1
by acetate	2.7	134	22.3	9	43 ± 4	32 ± 6	78 ± 2 [b]
by phosphate	1.6	134	19.0	5	69 ± 4	51 ± 8	87 ± 3
Cl^- replacement							
by isethionate	24	69	64	4	25 ± 3	44 ± 2	8 ± 3
by isethionate	24	47	87	4	33 ± 5	60 ± 3	11 ± 3
by isethionate	24	7.2	127	8	50 ± 3	89 ± 1	20 ± 5
Na^+ replacement	Na^+	Li^+					
	112	38		4	31 ± 3	16 ± 4	37 ± 4
	93	60		4	38 ± 5	28 ± 8	44 ± 4
	68	76		5	45 ± 2	28 ± 3	56 ± 3
	36	105		14	70 ± 3	58 ± 4	78 ± 2
Ouabain ($1 \cdot 10^{-6}$ M)				6	29 ± 2	15 ± 3	41 ± 3
($3 \cdot 10^{-6}$ M)				4	64 ± 7	42 ± 9	84 ± 3
($5 \cdot 10^{-6}$ M)				4	71 ± 6	62 ± 8	81 ± 4
($1 \cdot 10^{-5}$ M)				7	80 ± 2	66 ± 4	92 ± 2

[a] Calculated values assuming $Na^+ + K^+ = Cl^- + HCO_3^-$ + replacing anion.

[b] This value represents (HCO_3^- + acetate) secretion.

fluid does not change significantly, but a slight increase in the K^+ concentration is again observed. However, the increase of the K^+ concentration is also observed in the normal medium, suggesting that it might be due to leakage of K^+ from pancreatic or other cells in the bathed preparation.

When the results are expressed in units of secretory output of fluid, Cl^- and HCO_3^-, it becomes evident that all three parameters are decreased upon ion replacement or ouabain addition (Table II). This table represents data from experiments in which ouabain is added in four different concentrations varying from 10^{-6} to 10^{-5} M, experiments in which HCO_3^- is partly replaced by isethionate or fully replaced by acetate, phosphate or isethionate, experiments in which Cl^- is partly or fully replaced by isethionate and experiments in which part of the Na^+ is replaced by Li^+. Plotting these data in one graph as percentages inhibition of fluid, Cl^- and HCO_3^- secretion, it appears that the relation between the percentage inhibition of fluid secretion and Cl^-- or HCO_3^--secretion is about equal for all experiments in which HCO_3^- is replaced or in which Na^+ is replaced by Li^+ or in which ouabain is added (Fig. 4). In contrast, a completely different relation holds between the percentage inhibition of fluid secretion and Cl^-- or HCO_3^--secretion, when Cl^- is replaced by isethionate (Fig. 4). This figure also shows that the effects of replacing HCO_3^- and those of replacing Cl^- on the secretion of fluid and on the secretion of the accompanying anion (Cl^- or HCO_3^-) are entirely different. HCO_3^- replacement, Na^+ replacement and ouabain all greatly inhibit the secretion of fluid and Cl^- (maximally 95%), whereas Cl^- replacement inhibits fluid secretion by less than 55% and has only a minor effect on HCO_3^- secretion after replacement of a considerable part of the Cl^- in the medium.

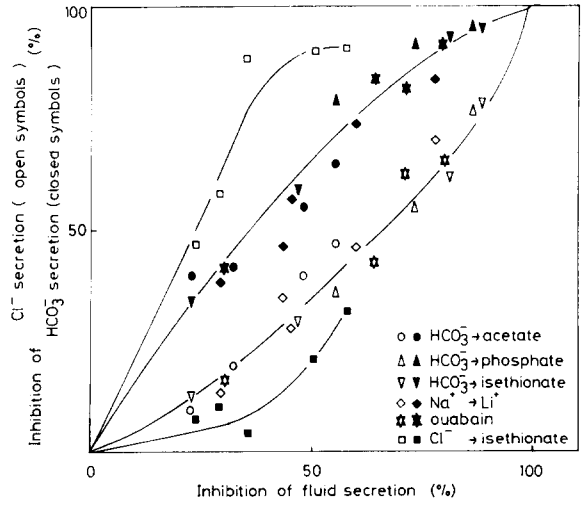

Fig. 4. Relationship between the inhibition of fluid secretion and the inhibition of HCO_3^- and Cl^- secretion. Data are taken from the experiments in which HCO_3^- is replaced by acetate (○, ●), phosphate (△, ▲) or isethionate (▽, ▼); Cl^- is replaced by isethionate (□, ■); Na^+ is replaced by Li^+ (◇, ◆); or ouabain (10^{-6}-10^{-5} M) is added (☆, ★). The results are expressed as percentages of the secretory rates in the control period, and represent mean values of 2–5 experiments.

Discussion

The anions bicarbonate and chloride are important for fluid secretion in the isolated rabbit pancreas, but they behave in different fashion. This is particularly shown in the experiments in which either of these anions is completely replaced by isethionate, for which anion the pancreas has a very low permeability. Replacement of bicarbonate leads to a nearly complete inhibition of fluid secretion, whereas replacement of chloride leads to only about 50% inhibition.

These findings are incompatible with a model in which a chloride-rich secretion from the acinar cells is mixed with a bicarbonate-rich secretion from the ductular cells, as is the case for the stimulated secretion in the rat [1,2]. It is more likely that the fluid secretion in the rabbit pancreas, as in the cat pancreas, is mainly or even entirely dependent on the secretion of HCO_3^- by one cell type, viz. the ductular cells. The low maximal bicarbonate concentration (82 mM) as compared to that obtained in the cat pancreas (140 mM; Ref. 6) may be explained by assuming that the chloride permeability in the rabbit pancreas is higher than in the cat. The lack of stimulation of fluid secretion in the rabbit pancreas by acetylcholine and cholecystokinin-pancreozymin, which stimulate enzyme secretion by the acinar cell, also supports the assumption that fluid is only secreted by one type of cells.

The requirement for bicarbonate is not absolute. As shown earlier by Swanson and Solomon

[15] for the isolated rabbit pancreas and by Case et al. [16] for the perfused cat pancreas, complete replacement of bicarbonate by acetate maintains fluid secretion, although at a lower rate. In the cat pancreas bicarbonate can be replaced by the anions of the weak organic acids sulfamerazine and glycodiazine. At least in the case of sulfamerazine, the concentration of the undissociated component appears to be the limiting factor in fluid secretion [4,17]. It has therefore been suggested that a Na^+-H^+ exchange carrier in the contraluminal membrane, driven by the Na^+ gradient, is the most likely mechanism underlying transcellular buffer and water secretion [15,17].

The difference in the effects of replacement by acetate, phosphate and isethionate found in our study seems to correlate with the different permeabilities for these anions. Acetate is secreted in a relatively high concentration as compared to phosphate and isethionate. The difference in the inhibitory effects of phosphate and isethionate on fluid secretion is not clear, since both anions appear hardly at all in the secretory fluid. Possibly, they have different effects on the cell pH and thus affect the residual fluid secretion rate differently. This residual fluid secretion is probably maintained by residual bicarbonate in the medium and metabolically derived CO_2, which keep the bicarbonate concentration in the secreted fluid from falling below a value of 30 mM.

The experiments in which chloride is replaced by isethionate indicate that chloride is not essential for fluid secretion, but that the presence of a permeable anion increases the fluid secretion rate. It is striking that the bicarbonate output remains unchanged, while the fluid secretion is inhibited by 35% upon reducing the chloride concentration from 130 to 50 mM. Only at very low concentrations of chloride (< 50 mM) in the bathing medium is the bicarbonate output reduced. This may be explained by assuming that a primary bicarbonate-rich fluid is secreted by the ductular cells, and that chloride appears in the secreted fluid by a secondary process, viz. by passive diffusion and/or exchange with bicarbonate. At low medium chloride concentrations, the decreased electrochemical gradient for bicarbonate between cell and lumen due to the increased luminal bicarbonate concentration may then lead to a decrease in bicarbonate secretion. However, we cannot rule out a direct role for chloride in facilitating bicarbonate transport into or out of the cell.

The effect of replacement of either bicarbonate or chloride on the secretion of the other anion is in accordance with the findings of Rothman and Brooks [18] and Swanson and Solomon [15] for the rabbit pancreas and by Case et al. [15] for the cat pancreas. In their experiments, replacement of bicarbonate inhibited secretion of chloride and this always occurred to a greater extent than that of bicarbonate upon replacement of chloride. These results indicate that bicarbonate is the primary secreted anion and that chloride secretion is regulated secondarily to bicarbonate secretion.

Our model of fluid secretion [8] assumes paracellular secretion of the cations Na^+ and K^+. Since Li^+ is transported to the secreted fluid in approximately equal concentration as present in the bathing medium, the paracellular secretion pathway for cations appears to be as permeable to Li^+ as to Na^+. Thus, an additional effect of Li^+ on anion secretion due to a different paracellular permeability is unlikely. Therefore, Li^+ has been chosen as the replacing cation. The inhibitory effect of this replacement on fluid and anion secretion suggests that there is a transport process underlying fluid secretion that is dependent on Na^+ for which Li^+ cannot substitute. A similar effect of substituting Na^+ by Li^+ was reported by Swanson and Solomon [15] and Case and Scratcherd [19].

One of our most interesting observations is that bicarbonate replacement by any of three anions, Na^+ replacement by Li^+ or addition of ouabain, all have the same effect on the relationship between bicarbonate or chloride secretion and fluid secretion. This strongly suggests that these experimental treatments act on the same transport mechanism, which is a critical, rate-limiting step in the fluid secretion process. The fact that for all these experiments the curve relating chloride output and fluid volume output is below the curve relating bicarbonate output and volume output (Fig. 4) could indicate a bicarbonate-chloride exchange mechanism in the main excretory duct, which causes the chloride concentration of the secreted fluid to rise at decreasing secretory rate. However, the micropuncture data of Caflish et al. [20] in the

rabbit pancreas in situ do not support the existence of such an exchange mechanism.

The findings reported in this paper suggest that pancreatic fluid secretion is based on a Na^+- and HCO_3^--dependent secretory mechanism. This is in accordance with our earlier model for fluid secretion by the ductular cell (cf. Ref. 8, Fig. 8). In this model the Na^+ gradient established by the ($Na^+ + K^+$)-ATPase system energizes a Na^+-H^+ exchange mechanism in the basolateral plasma membrane, which drives the conversion of CO_2 via H_2CO_3 to H^+ and HCO_3^-. The bicarbonate thus accumulated would leave the cell through the apical membrane by a neutral or electrogenic transport mechanism. This model can explain the secretion of various anions such as bicarbonate, acetate or even sulfamerazine and glycodiazine. The fact that 50 mM Cl^- is required for maximal bicarbonate secretion and 130 mM Cl^- for maximal fluid secretion suggests a dual role for chloride in electrolyte and fluid secretion: facilitating fluid secretion, and taking part in the transport of bicarbonate. How it does this, is not yet clear.

In conclusion, our results indicate that in the rabbit pancreas fluid secretion is driven by a Na^+-gradient-dependent mechanism present in the ductular cell, which maintains the transport of bicarbonate to the lumen. Chloride appears to facilitate fluid secretion, e.g. via its diffusion through an anion-permeable trans- or paracellular pathway, while Na^+ and K^+ are secreted secondarily to the anions through a paracellular route. Nevertheless, bicarbonate is the essential ion in pancreatic fluid secretion; its secretion triggers that of chloride, cations and water.

Acknowledgements

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